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Neurofibromatosis Type 2 (NF2)

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distribution unlimited**12b. DISTRIBUTION CODE****13. ABSTRACT (Maximum 200 Words)**

Neurofibromatosis 2 (NF2) is an autosomal disorder characterized by the development of multiple nervous system tumors such as vestibular schwannomas. The purpose of the study is to define the growth rate and clinical course of vestibular schwannomas in NF2-affected individuals. We will develop an international consortium of clinical centers with expertise in NF2, standardize the radiographic analysis of the vestibular schwannomas, assess the patients' audiological functioning, and analyze molecular, pathological, and clinical features of the disease over the course of 3 years.

We have enrolled nearly 50% of the target goal of 100 study participants. The difficulty enrolling patients has stemmed from a protracted informed consent approval process, one co-PI leaving a core site, and a lengthy process to ensure that MRI scanning facilities are compatible with WorldCare's systems. We have addressed the enrollment problem by lengthening the enrollment window to January 31, 2000 and expanded the inclusion criteria to include NF2-affected family members. Baseline data have been collected on 65% and 52% of the enrolled patients for audiological and MRI data respectively. We have made good progress toward completion of the first year's goals and anticipate few problems with the collection of 1 year follow-up data.

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FOREWORD

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 10/29/99

PI - Signature Date

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Introduction

Neurofibromatosis 2 (NF-2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All patients inevitably develop bilateral vestibular schwannomas that lead to total deafness and death if not treated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to vestibular schwannomas and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of natural history of vestibular schwannomas, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study is to define the growth rate and clinical course of vestibular schwannomas in NF-2-affected individuals. We seek to accomplish this goal through the following steps.

1. Develop an international consortium of clinical centers and expertise in NF-2.
2. Develop standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.
3. Analyze standardized prospective neurophysiological/audiological results from NF-2 patients.
4. Examination of molecular, pathological and clinical features which may predict tumor behavior.

This study will lead to a better understanding of the natural history and clinical course of vestibular schwannomas in NF2. The knowledge gained from this study will allow anticipatory guidance of newly diagnosed patients and better recommendations regarding current treatment. The framework of clinical centers, data management and scientific expertise established during this project will form the core for future studies investigating other aspects of natural history of NF-2 and therapeutic treatment trials in NF-2.

Body

STATEMENT OF WORK

Natural History of Vestibular Schwannomas in Neurofibromatosis 2 (NF2)

Task 1. Development of an international consortium of clinical centers and expertise in NF2 and overall project activities.

a. Development of communication infrastructure for NF2 consortium members (month 1); Completed

A complete directory listing the site Co-Principal Investigators, Clinical Coordinators and other researchers involved in the NF2 study was created and distributed to study members. The directory, which presents phone numbers, fax numbers, addresses and email addresses, allows study members to communicate with each other when necessary.

Correspondence between centers is also transmitted through FAX. A FAX machine at the House Ear Institute (HEI) is solely dedicated to the NF2 study and a group-dial function allows it to automatically FAX to all the study members.

A List Server was established to facilitate rapid communication between the consortium sites through email. Two List Servers were created: one holds the email addresses of the NF2 study Steering Committee and the other holds the email addresses of the researchers at the Patient Collection Centers. Using the list server, a list member can quickly correspond to the entire group using one email address.

Information regarding video-conferencing capabilities at each consortium site was ascertained and this mode of communication might be utilized in the future. Currently, cost is the major factor limiting this type of communication.

Beginning with the month of February 1999, HEI initiated distribution of a Monthly Progress Report to the consortium sites and study members: Central Laboratory Centers, Patient Collection Centers, and Steering Committee. These reports provide updates on activities at specific consortium sites as well as present an overview of the project's progress.

A website was created to facilitate communication and data transfer between Patient Collection Centers and the central data management center at House Ear Institute (HEI). This website can be found at <http://www.hei.org/NH/main.htm>. The site has been guarded by a password given to researchers participating in the study. This website allows clinical coordinators to view a spreadsheet showing what information has been received by HEI and what is pending submission. The information displayed on the website is updated on a weekly basis.

b. Development of centralized data management system (months 1-3); Completed

A coordinated system for collecting and transmitting study data was established. A procedure manual documenting all study procedures was established and distributed to all Central Laboratory Centers and Patient Collection Centers.

As detailed in this Procedure Manual, HEI serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators initially FAX all completed data forms to HEI and later mail all original forms at the end of the month. A Central Tracking

System was established at HEI to track each subject and assure the consistent inflow of data from each site.

All study data that are sent by a Patient Collection Center and received by HEI is recorded on the site's Data Log. Files for each subject have been created and kept in a locked cabinet. Each subject file holds its own log on which to record incoming data.

Zoreh Davanipour, Ph.D. left the House Ear Institute during the summer of 1999. Laurel Fisher, Ph.D. has assumed responsibility for the statistical data and management center. Dr. Fisher comes to HEI with an extensive history of coordinating data for multi-institutional, multi-national trials. Her biosketch is attached in the appendix. With the assistance of the statistical analysis and data management team at HEI, Dr. Fisher was able to assume the responsibilities of Dr. Davanipour, specifically for the centralized tracking system. She has worked closely with Dr. Wendy Mack, the biostatistical consultant for the project.

c. Development of infrastructure within participating clinical centers to identify and recruit NF2 patients (months 1-3); Completed

A Clinical Coordinator has been identified at each site, and the infrastructure has been established at each Patient Collection Center. The study protocol and the consent forms have been submitted to local Institutional Review Boards at each site for approval. Each Patient Collection Center has an established NF2 database and/or has access to medical records with information on all the NF2 patients followed at their site. These were the basic sources for initial patient screening and identification.

Some Patient Collection Centers initiated patient recruitment projects to identify additional subjects outside of their immediate patient population. HEI submitted articles which were published in widely-read NF2 publications such as the *NNFF Newsletter* and the *NF2 Review*. A summary of the study was posted on several web sites including that of House Ear Institute, the NF2Crew, the National Neurofibromatosis Foundation, Centerwatch, and the National Cancer Institute.

Solicitation letters were also mailed to approximately 1,400 neurologists and neurosurgeons in Southern California and approximately 400 members of the American Neurotology Society, requesting referrals of potential subjects. These activities have resulted in responses from 17 NF2 patients and approximately 49 physicians. Through these efforts, several patients have been referred to the study and four sites are preparing to join the consortium as satellite sites. The patients and possible study centers have been surveyed to evaluate their level of participation before processing with invitations to join the study.

Mount Sinai Medical Center also pursued patient recruitment activities to increase their number of potential subjects. The site's Co-Principal Investigator at the time, Frank Lieberman, M.D., at the site discussed the NF2 Natural History study with area physicians following NF2 patients. Mount Sinai also posted the study on the NF2 patient-run internet chat room. Four potential patients were identified. Dr. Frank Lieberman left Mount Sinai and moved to the University of Pittsburgh. He is currently in the process of establishing his practice at the University of Pittsburgh, but has indicated a willingness to try and recruit patients from this site. Dr. Lieberman remains an active supporter of this project and we anticipate he will enroll patients at this site soon. Allan Rubenstein, M.D. has accepted the position of Co-Principal Investigator at the Mount Sinai site.

d. Train clinical centers' staff in study protocol (months 1-3); Completed

A Steering Committee/Training meeting was held December 4, 1998 to review the study protocol with all Co-Principal Investigators.

The protocol for the audiology exams was distributed to the study audiologists at each Patient Collection Center and any questions were directed to the Audiology Study Coordinator at HEI. The protocol for collecting MRI data was outlined in the *Standard Operating Procedure (SOP)*, written by WorldCare, Inc. This *SOP* was distributed to the Patient Collection Centers and their associated radiology sites. The NF2 Natural History grant protocol and Procedure Manual were distributed to each Co-Principal Investigator and Clinical Coordinator at each site. HEI maintains ongoing telephone discussions with the Clinical Coordinators to facilitate the study.

e. Identification and enrollment of 100 NF2 patients (months 1-3); In Progress

Clinical Coordinators at each Patient Collection Center have screened their patient population and identified potential subjects for the NF2 Natural History study.

Table 1 below summarizes the current number of NF2 patients at each site who qualify for the study and are enrolled.

Table 1: Patient Enrollment

Patient Collection Center	Location	Total Identified	Patients Qualified	Patients Enrolled	Qualified Family
House Ear Institute	Los Angeles, CA	299	36	18	6
MGH	Charlestown, MA	31	16	16	
Mt. Sinai	New York, NY	11	4	0	0
St. Mary's	Manchester, UK	64	17	0	6
Klinikum Nord Ochsenszoll	Hamburg, Germany	20	10	10*	
Additional Sites Recruited					
Lawrence Grobman, MD	Miami, Florida	1	1	0	
Henry Ford Hospital: Monsell	Detroit, MI	12	TBD	0	
Thomas Jefferson Univ.: Willcox	Philadelphia, PA	1	1	0	
Helsinki Univ. Hospital: Vasama	Helsinki, Finland	2	2	2	
Univ. Texas, Houston: Chang	Houston, TX	2	2	0	
Melbourne University: Briggs	Melbourne, Australia	13	2	2	7
Pittsburgh Ear Assoc: Chen	Pittsburgh, PA	1	1	0	
Ohio State Univ. Hospital: Welling	Columbus, OH	4	4	0	
Kaiser Permanente: Cueva	San Diego, CA	2	2	0	
Nagoya University: Kiyoshi	Nagoya, Japan	3	3	0	
Total		466	101	48	14

* will be enrolled once KNO receives approval from the Army.

"Total Identified" signifies patients whose chart were reviewed.

"Patients Qualified" signifies patients meeting inclusion criteria.

"Patients Enrolled" signifies consented patients.

"Qualified Family" signifies patients who meet criteria, but have a family member already enrolled.

The major problem of this study has been patient accrual. The main reason for this low recruitment number is the unanticipated delay of Institutional Review Board (IRB) approval. When the proposal was submitted, it was the plan of the Principal Investigator to have IRB approval performed at each site prior to the initiation of the study. Unfortunately, processing of the consent forms has considerably delayed patient enrollment. The consent forms for the study were initially approved by House Ear Institute's local IRB on February 12, 1998. The Department of Defense did not provide final approval of the study consent forms until October 14, 1998. Once these were approved, the consent forms were distributed to all Patient Collection Centers and immediately submitted to the locals IRBs. Unfortunately, there was a delay in receiving approval from each local IRB and the Human Subjects Protection Division of the U.S. Army Medical Research and Materiels Command (UASMRMC). There has been quite a bit of turnover in the

Human Subjects Protection Division of the US Army Research and Materiel Command. We have worked with several individuals in this office, trying to speed up the approval process.

We have recruited additional Patient Collection Centers, as specified in the protocol. We are in the process of securing IRB and Army approval of informed consent forms for these additional sites.

The current status of IRB approval is listed below.

Table 2: IRB approval

Patient Collection Centers	IRB Approval	US Army Approval
House Ear Institute	February 12, 1998	October 30, 1999
MGH	March 17, 1999	September 23, 1999 (conditional approval)
Mt. Sinai	December 4, 1998	September 27, 1999 (conditional approval)
St. Mary's	February 18, 1999	September 23, 1999 (conditional approval)
Klinikum Nord Ochsenzoll	January 12, 1999	Pending

A second reason for the slower than expected enrollment is difficulty enrolling patients from the Mount Sinai Medical Center. Mount Sinai was expected to enroll upwards of 20 patients and thus far, no patient has been enrolled. The departure of Co-Principal Investigator, Dr. Lieberman, has additionally complicated the situation.

The Steering Committee meeting discussed ways to increase subject enrollment. It was suggested that the inclusion criteria be expanded to include patients with a diagnosis prior to 1993. This idea was discarded due to the difficulty with gaining access to retrospective data, especially MRI data.

The Steering Committee settled on three ways to increase enrollment: 1) Expand the enrollment window to January 31, 2000, 2) Recruit additional study sites, 3) Expand the inclusion criteria to allow recruitment of family members.

The original protocol stipulates that family members of study participants are excluded from participation. The Steering Committee in conjunction with the statistical consultant, Wendy Mack, Ph.D., suggested expanding the inclusion criteria to now include NF2-affected family members of participants. Expansion of the inclusion criteria may result in an additional 20 subjects participating. We anticipate full enrollment by January 31, 2000.

f. Collection of baseline individual patient data (months 2-6); In Progress

This step has been delayed pending IRB approval at study sites. Baseline MRI data have been collected on 13 patients and 10 baseline audiology examinations have been performed. Specifics of data collection are listed under tasks 2, 3, and 4.

g. Collection and computerization of yearly follow-up individual patient data (months 12-35); In Progress

A computerized monitoring system has been established that interacts with the patient database. Monthly reminders are sent to each clinical coordinator, alerting them to upcoming examinations that require scheduling. No follow-up data has been collected as one year has not passed for any enrolled patient. The first patient was enrolled on January 6, 1999.

- h. Preparation of material for future clinical treatment outcome study (months 25-36); Pending**
While this topic is planned for the future, initial discussions have occurred regarding future clinical treatment trials. The recent request for proposals (RFP) from the USAMRMC for treatment trials was discussed by the steering committee. At this time, the steering committee felt that not enough was known about the natural history and there were currently no good drugs available for NF2 specific treatment trials. The group decided to not submit a proposal at this time. A major concern for instituting a treatment trial was that measuring systems had not been developed to determine treatment effect and assure that tumor growth change over time was not significantly different from the natural history.
- i. Data editing, corrections, updates and management (months 4-35); In progress**
Data editing, corrections, and updating is an ongoing process as data are submitted. The clinical coordinators review the study data before forwarding it to the data management center at HEI. The HEI research assistant and a supervisor perform another review of the data. Clinical Coordinators are asked to re-submit any data that is problematic
- j. Data analysis (months 6-12, 22-24, 34-36); Pending**
Data analysis will be preformed once the enrollment figure has been reached. A one-year analysis will be performed once 100 patients have been enrolled in the study. Initial analysis will include review of baseline and retrospective data.
- k. Manuscript preparation (months 10-12, 22-24, 34-36); Pending**
Manuscripts will be prepared once data analysis has been completed.

Task 2. Standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.

- a. Development of standard operating procedure for digital analysis of MRIs (months 1-3); Completed**
A standard operating procedure manual (SOP) is complete for both the Patient Collection Centers and the WorldCare Measurement Center. The WorldCare Patient Collection Center SOP was merged with the HEI procedure manual and has been distributed to the clinical coordinators at each Patient Collection Center.
- b. Set-up for communication of data to the statistical analysis and data management center (months 1-3); Completed**
There are two methods of data transfer to the Statistical Analysis and Data Management Center at HEI. All measurement data recorded on the WorldCare Measurement Center MRI data forms is transferred via mail until an electronic means of data entry becomes available. All image data is transferred to HEI via FTP. HEI was provided with a viewing system for these FTP images complete with the measurement and viewing software Cheshire™. Both means of data transfer have been successfully utilized to send patient data.
- c. Preparation of facilities at WorldCare, Inc. (months 1-3); Completed**
A private suite for the NF2 Natural History Study has been prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data have been used for the collection and analysis of patient data. Also, the filing system, logbooks, and patient database are established to accept and track the workflow of patient data.
- d. Preparation of MRI facility to transmit data (months 1-3); Initial Stage Completed, Additional Sites: Ongoing**

Each of the MRI facilities affiliated with the original five Patient Collection Centers has transmitted test data to WorldCare via optical disk or FTP. Four of the facilities use hardware and software compatible with WorldCare's acquisition and analysis systems. The fifth facility is re-sending test data in a format that is compatible with WorldCare systems. Thus, the initial task to certify a MRI facility at the study sites is complete.

As subjects were enrolled, the number of MRI facilities required to provide data have expanded. As stated in the study protocol, each MRI facility had to become familiar with the scanning protocol, agree to perform the scans as specified, and have their MRI equipment assessed for compatibility with WorldCare. To date, 33 MRI facilities have been contacted to complete the site survey and send sample data. Only one site has been disqualified on the basis of equipment incompatibilities.

The process of certifying MRI facilities to send study data will be ongoing.

e. Perform qualitative and quantitative analysis of MRIs (months 4-33); In Progress

Both qualitative and quantitative analyses have been performed on 13 enrolled patients. These patients were scanned and collected within the study protocol parameters. The images were collected and measured by a WorldCare Measurement Center Technician providing both linear and 3D volumetric measurements of the acoustic neuromas. These measurements were reviewed by a sub-specialist radiologist, and the finalized measured images and the results of the volumetric analysis were forwarded to Dr. Slattery at the HEI for review. The official study forms were forwarded to the NF2 Research Assistant at the Statistical Analysis and Data Management Center at HEI for entry into the study database.

f. Collection of MRI scan obtained prior to initiation of study (months 2-6); In Progress

MRI scans for 39 previous patient visits have been obtained on 25 subjects. This process has been delayed due to the IRB approval of consent forms. The clinical coordinators are rapidly trying to obtain all retrospective films as patients are enrolled to catch up from the time lost due to the delay of the informed consent. The WorldCare Measurement Center systems have been used to digitize and analyze these prior MRI scans for the collection and processing of this patient data.

g. Collection of yearly MRI material (months 1-35); In Progress

13 officially enrolled patients have received their baseline study scans that were collected by the WorldCare Measurement Center. WorldCare has sent the data forms to HEI. An additional 12 subjects have been scheduled for their baseline MRI scans in the next two months.

h. Transmitting volumetric data to the statistical analysis and data management center (months 4-35); In Progress

Both measurement and image volumetric data for the first 13 patients reviewed has been transmitted from WorldCare to the Statistical Analysis and Data Management Center at HEI. The image data was transferred via FTP to a review station at HEI equipped with the measurement and viewing software Cheshire™. The measurement data for both the technician and radiologist was recorded on MRI data forms and sent via mail to HEI.

Task 3. Standardized prospective neurophysiological/audiological analysis of patients.

a. Training clinical centers on audiology protocol (months 1-3); Completed

The audiology protocol was distributed to the Patient Collection Centers and questions were directed to the Audiology Center Coordinator. Study audiologists have been identified at each of the patient collection centers that have agreed to conduct the examinations.

b. Development of communication pathways for audiology data management (months 1-3); Completed

The Statistical Analysis and Data Management/Coordinating Center at HEI manages the audiology data in the same manner as other study data. As outlined in the study Procedure Manual, completed forms are initially faxed to the HEI Research Assistant and the original is mailed to HEI at the end of each month. Once the Research Assistant receives the completed *Audiology Data Form*, it is forwarded to the Audiology Center Coordinator at HEI to be reviewed. The data are then entered into the database.

c. Collection of audiometric testing performed prior to initiation of study (months 2-6);

Retrospective audiological data have been collected from 121 different patient visits for 31 subjects. Collection of retrospective data is an ongoing process.

d. Collection of baseline audiometric data (months 2-6); In Progress

Baseline audiometric data for 21 subjects have been collected to date. An additional 10 subjects have been scheduled for their baseline audiological examinations in the next two months.

e. Collection of follow-up yearly audiometric data (months 1-35);

No follow-up data has been collected as one year has not passed for any enrolled patient. The first patient was enrolled on January 6, 1999.

Task 4. Examination of molecular, pathological and clinical features which may predict tumor behavior.

a. Standardization of methods for pathological and molecular analysis (months 1-3); Completed

A standard protocol and report has been established for review of pathological specimens and for the molecular genetic analysis.

b. Establish method of data acquisition and transfer to the statistical analysis and data management center (months 1-3); Completed

As outlined in the NF2 Natural History Procedure Manual, data are acquired and recorded on the data forms which are then faxed and mailed to House Ear Institute.

c. Collection of pathological samples from tumors removed prior to initiation of study for analysis (months 4-9); In Progress

13 tumor specimens, including H & E slides, unstained slides, and pathology reports have been obtained on 13 patients enrolled in the study. Two additional specimens were retrieved and required H & E sections to be stained and unstained sections to be cut. All cases have been stained for Ki-67 with MIBI antibodies using positive and negative controls (tonsils). Image analysis has not yet been performed to quantitate the staining, but will be performed once additional cases have been received and stained.

The assay for Neurofilament antibodies to assess trapped nerve fibers is in the process of optimization. Data sheets will be filled out and sent to HEI once the staining has been completed and once the slides have been reviewed by Dr. Louis and Dr. Stemmer-Rachamimov. We anticipate that the standard histopathology review of these cases will be completed the end of November.

Blood has been obtained from all patients enrolled in the study and have been submitted to Dr. MacCollin's lab for genetic analysis. Genetic analysis has been completed on 18 subjects.

d. Collection of pathological samples from tumors removed during the course of the study (months 1-35); In progress

To date, no patient has required tumor removal once the patient has been enrolled in the study.

Key Research Accomplishments

- Development of an international consortium of clinical centers and expertise in NF-2.
- Establishment of standardized study protocol for multi-institutional, multi-national natural history study.
- Development of NF-2 specific database which includes clinical, radiographical, audiometrical, pathological and molecular biology/genetic information.
- Development of standard operating procedure for digital analysis of MRI's utilizing information from a variety of different MRI brand machines.
- Establishment of NF-2 specific pathology specimen bank.
- Development of NF-2 molecular biology database.

Reportable Outcomes

No reportable outcomes were anticipated during the initial start-up phase of the study.

None have occurred.

Conclusions

The infrastructure necessary for this project to be successful has been assembled. Subject enrollment has been difficult due to the delay in achieving approval of the informed consent forms for each institution by the Army and a Co-Principal Investigator leaving one of the core patient collection sites. In addition, much effort was given to ensuring that the MRI facilities used by study participants are compatible with WorldCare's systems. The problem of slow enrollment has been addressed through recruitment of additional sites, expansion of the inclusion criteria, and expanding the time for enrollment to occur. Despite these difficulties by the end of the calendar year, baseline audiological data will be collected on 65% of the enrolled subjects and 52% of the subjects will have undergone their baseline MRI scans. It is anticipated that full patient enrollment will be complete by January 31, 2000.

References:

None

Appendix A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME Laurel M. Fisher, Ph.D.		POSITION TITLE Advanced Research Associate, Clinical Studies, House Ear Institute	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
California State University, Fresno, CA.	B.A.	1982	Psychology
California State University, Fresno, CA.	M.A.	1985	Psychology
University of Southern California, Los Angeles, CA.	Ph.D.	1993	Psychology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL POSITIONS:

1999-present; Advanced Research Associate, House Ear Institute
1996-1999; Biostatistician, Clinical Research Department, Advanced Bionics Corporation
1994-1996; Postdoctoral Fellow, UCLA School of Medicine
1993-1996; Adjunct Professor, Fuller Theological Seminary: School of Psychology

AWARDS AND OTHER PROFESSIONAL ACTIVITIES:**Professional Associations**

American Academy of Otolaryngology-Head Neck Surgery (AAO-HNS) *PENDING*
Society for Clinical Trials, Inc. *PENDING*
American Statistical Association-Biopharmaceutical Section
American Psychological Association
American Psychological Society

RELEVANT PUBLICATIONS: (PARTIAL LISTING)**Articles:**

Osberger MJ, Fisher LM. Preoperative predictors of postoperative implant performance in children. 7th *Symposium of Cochlear Implants in Children*. In press.

Geier L, Barker M, Fisher LM, Opie J. The effect of long-term deafness on speech recognition in postlingually deafened adult CLARION→ cochlear implant users. *Ann Otol Rhinol Laryngol* 1999;108(suppl 177):80-83.

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RELEVANT PUBLICATIONS: (PARTIAL LISTING) CONTINUED

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Invited Presentations:

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